REDACTED - PUBLIC VERSION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SANOFI-AVENTIS DEUTSCHLAND GMBH, AVENTIS PHARMA S.A., ABBOTT GMBH & CO. KG, and ABBOTT LABORATORIES, Plaintiffs, v. GLENMARK PHARMACEUTICALS INC., USA, and GLENMARK PHARMACEUTICALS LTD., Defendants.	Hon. Dennis M. Cavanaugh, U.S.D.J. Hon. Mark Falk, U.S.M.J. Civil Action No. 07-CV-05855 (DMC-MF) ~~FILED UNDER SEAL~~

DECLARATION OF CLIVE ROSENDORFF

I. QUALIFICATIONS

1. I am currently Professor, Department of Medicine, the Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine of New York University, New York, NY and Medical Program, James J. Peters VA Medical Center, Bronx, NY. I am also currently an attending physician (internal medicine and cardiology) at Mount Sinai Hospital and the Director of Graduate Medical Education at James J. Peters VA Medical Center in the Bronx, NY. I am a U.S. citizen.

2. I received an MB BCh (equivalent to M.D. in the U.S.) from the University of Witwatersrand, Johannesburg, South Africa in 1962, and a Ph.D. from the University of London in 1969.

3. I also have the DScMed degree. I am an elected Fellow of the Royal Society (SA), a Fellow of the Royal College of Physicians of London, a Fellow of the American College

of Physicians, a Fellow of the American College of Cardiology, and a Fellow of the American Heart Association. My clinical and research interests have revolved around the treatment of cardiovascular disease. I have authored or co-authored more than 160 peer-reviewed research papers, numerous other abstracts and short papers, 48 book chapters, and authored or edited two textbooks in that field..

4. Over my career, I have treated many patients for hypertension, and a substantial portion of my research efforts have focused on understanding and treating that disease. My curriculum vitae is attached as Exh. A.

II. BACKGROUND OF ANTIHYPERTENSIVE THERAPY

5. Hypertension or high blood pressure is a common condition that affects millions of Americans. It is a major risk factor for cardiovascular disease, heart failure and stroke. For many years, medical scientists have sought drug therapies for hypertension, and have developed a variety of drug products.

6. Several different physiological processes affect blood pressure. Hypertension can therefore be treated with a variety of different strategies or combinations of strategies, depending on the particular patient. For example, diuretics were among the earliest orally effective antihypertensive drugs. Diuretics increase the rate of excretion of sodium and water by the kidneys, but also directly relax the smooth muscle cells in arteries, thus lowering the blood pressure. Diuretics are still widely used for hypertension treatment. Other oral treatments were introduced later, such as, for example, "alpha blockers" and "beta blockers."

7. More recently, medical scientists developed a class of compounds for treatment of hypertension called "angiotensin-converting enzyme inhibitors" or "ACE inhibitors." These compounds interfere with the activity of an enzyme that converts angiotensin I to angiotensin II.

Angiotensin II causes constriction of blood vessels, so that interfering with its production lessens blood vessel constriction, thereby lowering blood pressure. The first ACE inhibitor marketed in the United States was captopril, which was commercially introduced in 1981 as CAPOTEN, and was prescribed for the treatment of hypertension. One disadvantage of captopril was its short half-life, which required twice or three times daily administration. In addition, captopril exhibited certain undesirable side effects that were attributed to the sulfhydryl group in the captopril molecule. Although these side effects were dose-related and could be reduced by lower dosing, they nevertheless remained an issue for some patients. Notwithstanding these disadvantages, captopril was widely prescribed for treatment of hypertension, and was a significant commercial success.

8. Another ACE inhibitor, enalapril, was introduced in 1985 as VASOTEC. Lisinopril was approved in the U.S. in 1987 as PRINIVIL. Quinapril (ACCUPRIL) and ramipril (ALTACE) were approved in 1991, benazapril (LOTENSIN) was approved in 1991, and trandolapril (MAVIK) was approved in 1996. None of these compounds included the sulfhydryl group in their molecular structures, and all were longer-acting than captopril. Of course, the technical literature contained a great deal of information about these compounds well before their FDA approval and market introduction. Clinical reports showing the blood pressure lowering effects of captopril, enalapril, lisinopril, ramipril and quinapril in human patients were published prior to October 1986.

9. Another class of compounds called "calcium antagonists" or "calcium channel blockers" work by decreasing the amount of calcium that enters the smooth muscle of blood vessels, which leads to less contraction, an increase in blood vessel diameter and a lowering of blood pressure. Before October 1986, several calcium channel blockers had been evaluated in

animal or human studies including diltiazem, nifedipine, felodopine, nitrendipine, nicardipine and verapamil. Diltiazem, verapamil and nifedipine had been used in human studies for the treatment of hypertension with a sustained release or slow release formulation. Nifedipene had been approved in Europe for the treatment of hypertension, and physicians in the United States recognized that calcium antagonists were effective in treating hypertension and prescribed those drugs for that purpose.

10. As of 1986, much was known about the mechanism of action of ACE inhibitors, although subsequent studies have provided further insights. In particular, it was known that the sulfhydryl group in captopril interacts with the Zn^{+2} atom in ACE, thereby interfering with its ability to convert angiotensin I to angiotensin II. Enalapril and quinapril were known to act by competing for binding sites on the ACE molecule. Medical researchers had developed *in vitro* and *in vivo* models for testing for ACE inhibition of drug candidates.

11. Before October 1986, persons skilled in the art understood that regardless of their molecular structure, ACE inhibitors compete with angiotensin in binding to ACE, and that they inhibit the conversion of angiotensin I into the pressor-active angiotensin II. The person of ordinary skill in the art would have viewed captopril, enalapril, quinapril and ramipril as belonging to the same class of drugs—ACE inhibitors—based on their ability to inhibit the conversion of angiotensin I into angiotensin II.

12. In 1986, persons skilled in the art understood that the mechanism of action of ACE inhibitors was independent from that of the calcium antagonists. Dr. Piepho's citation of a paper I published in 1996 (JACC **28**, No. 4, 803–12 (1996) (Skiles dec., Exh. 23)[1] is misplaced.

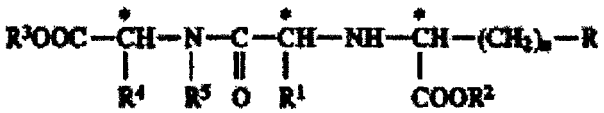
[1] "Skiles dec." refers to the Declaration of Seth A. Skiles dated May 14, 2010.

(*See* Piepho dec., ¶¶ 53-55.)[2] First, the information he cites was not known in 1986, so it could not have influenced a person of ordinary skill in the art at the time. Second, the paper said nothing about the interaction of ACE inhibitors and calcium channels. The angiotensin 1 (AT1) receptor may interact with the calcium channels but the AT1 receptor is not the site of action of ACE inhibitors. Even if there was interaction between the AT1 receptor and calcium channels, it is almost certainly trivial in magnitude compared to the effects via the established transduction pathway. The inevitable conclusion is that the mechanisms of action of ACE inhibitors and calcium channel are totally independent.

13. It has long been apparent to medical scientists that several different physiological mechanisms influence blood pressure, and each can be targeted by drug therapy independently of the others. Thus, medical scientists before October 1986 had developed combination therapies that use two or more different antihypertensive drugs, each of which targets a different mechanism.

III. THE '244 PATENT

14. I have reviewed U.S. Patent 5,721,244 ("the '244 patent"; Exh. B hereto.) The '244 patent describes and claims a combination therapy for hypertension. The claimed composition is a combination of an ACE inhibitor and a calcium antagonist. The patent defines the ACE inhibitor by a particular formula, set forth below:



(I)

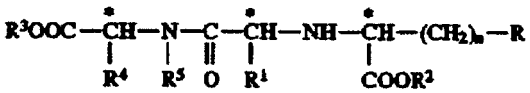
[2] "Piepho dec." refers to the Declaration of Robert W. Piepho dated May 14, 2010.

This formula, with R, R^1, R^2, R^3, R^4 and R^5 as defined in the patent, encompasses many individual compounds, and their "physiologically acceptable salts." The patent makes clear that Formula I encompasses quinapril, trandolapril, and ramipril. (Col. 6, lines 60-67.) It does not, however, encompass the ACE inhibitors captopril, enalapril or lisinopril.

15. Claim 1 defines a pharmaceutical composition whose active ingredients are an ACE inhibitor chosen from a subset of the formula defined above and any calcium antagonist:

1. A pharmaceutical composition comprising:

(a) an angiotensin-converting enzyme inhibitor (ACE inhibitor) of the formula I



(I)

in which

n=1 or 2,

R=hydrogen,

an aliphatic radical with 1–8 carbon atoms,
an alicyclic radical with 3–9 carbon atoms, or
an aromatic radical with 6–12 carbon atoms,
an araliphatic radical with 7–14 carbon atoms,
an alicyclic-aliphatic radical with 7–14 carbon atoms,
a radical OR^a or SR^a, wherein

R^a represents an aliphatic radical with 1–4 carbon atoms or an aromatic radical with 6–12 carbon atoms,

R^1 is hydrogen,

an aliphatic radical with 1–6 carbon atoms,
an alicyclic radical with 3–9 carbon atoms,
an alicyclic-aliphatic radical with 4–12 carbon atoms,
an aromatic radical with 6–12 carbon atoms,
an araliphatic radical with 7–16 carbon atoms or
the side chain, protected if necessary, of a naturally occurring α-amino acid,

R^2 and R^3 are the same or different and are hydrogen, an aliphatic radical with 1–6 carbon atoms, an alicyclic radical with 3–9 carbon atoms, an aromatic radical with 6–12 carbon atoms, an araliphatic radical with 7–16 carbon atoms and R^4 and R^5 together with the atoms carrying them form a heterocyclic bicyclic or tricyclic ring system selected from tetrahydroisoquinoline, decahydroisoquinoline, octahydroindole, 2-azaspiro[4,5]decane, 2-azaspiro[4,4]nonane, spiro[(bicyclo[2,2,1]heptane)-2,3'-pyrrolidine], spiro [(bicyclo[2,2,2]octane)-2,3'-pyrrolidine], 2-azatricyclo[4,3,0,$1^{6,9}$]decane, decahydrocyclophepta[b]pyrrole, octahydroisoindole, octahydrocyclocopenta[c]pyrrole, 2,2,3a,4,5,7a-hexahydroindole, 2-azabicyclo[3,1,0]-hexane, hexahydrocyclopenta[b]pyrrole, or a physiologically acceptable salt thereof, and

(b) a calcium antagonist or a physiologically acceptable salt thereof;

wherein said ACE inhibitor and said calcium antagonist are present in said composition in amounts effective for treating hypertension;

and with the proviso that when said calcium antagonist is 4-(2,3-dichlorophenyl)-2,6-dimethyl-3-methoxycarbonyl-5-ethoxycarbonyl-1,4-dihydropyridine (felodipine), said angiotensin-converting enzyme inhibitor is not 1-(2S,3aR,7aS)-octahydro[1H]indole-2-S-carboxylic acid (trandolapril).

16. Most of the text of the claim consists of the definition of the ACE inhibitors that can form part of the claimed composition. Those ACE inhibitors include quinapril and trandolapril, with the proviso that when the calcium antagonist is felodipine, the ACE inhibitor is not trandolapril. The definition of the calcium antagonist is unrestricted to any particular compound or group of compounds.

17. The '244 patent does not contain any experimental data showing the efficacy of the claimed combination.

IV. THE PRIOR ART DISCLOSED ACE INHIBITOR CALCIUM ANTAGONIST COMBINATIONS

18. As of October 1986 several ACE inhibitors had been approved by the FDA or were in clinical development. Captopril and enalapril had been approved in 1981 and 1985 respectively. *See* Drug Facts and Comparisons, 1995 Edition. (Exh. C hereto.) Lisinopril was well along in clinical trials and was approved in 1987. *Id.* Quinapril and ramipril were in clinical trials and had been shown to lower blood pressure in human patients. A few others had been tried in volunteers, but I do not believe that any data had been reported showing their use in patients. Of the ACE inhibitors that had been tested in patients, the prior art describes using the first three, captopril, enalapril, and lisinopril, in combination with a calcium antagonist.

19. Shortly after captopril became available, researchers recognized the possibility of combining it with calcium antagonists to treat hypertension. In 1983, M. Stornello *et al.*, Supp. III Hypertension Vol. 5, No. 5, III 154-156, Abstract, September-October 1983 (Exh. D hereto), described a study in which hypertensive patients received the ACE inhibitor captopril in combination with the calcium antagonist nifedipine. The study data revealed that "captopril and nifedipine exert an additive effect on blood pressure and renin." (*Id.*, Abstract.) The authors concluded that:

> These findings suggest that the two drugs exert an additive hypotensive action, which can tentatively be explained by the fact that captopril can either reduce SNS activation or block the cardiovascular effect of renin stimulation induced by nifedipine.
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> . . . the findings that captopril and nifedipine exert an additive hypotensive effect, indicate that these two drugs can be usefully combined in the treatment of hypertensive patients.

(*Id.*, III-155, III-156.)

20. In 1985, R.M.L. Brouwer *et al.*, J. Cardiovascular Pharmacol. 7, Supp. 1, S88-91 (1985) (Exh. E hereto), described a study in which hypertensive patients were treated with a combination of the ACE inhibitor captopril and a calcium antagonist, either verapamil or nitrendipine. The patients' hypertension had not been adequately controlled by prior therapy, but the combination of captopril and the calcium antagonist brought their diastolic blood pressure to the desired level. Dr. Carey states that in the Brouwer study, the combination therapy did not overcome the excess fluid and weight gain in "some patients" for whom diuretic therapy was discontinued. (*See* Carey dec., ¶ 13.)[3] Dr. Carey is wrong. In fact, the paper states:

> All patients completed this study without unwanted side effects which would have prompted discontinuation of the therapy. One patient complained of transient ankle edema and another of transient headaches.

(Brouwer at p. S90.) Ankle edema is a common side effect of calcium antagonists. The fluid retention and weight gain to which Brouwer referred were in other patients, not in this study, particularly those patients who exhibited venous insufficiency or had just ceased long term diuretic therapy.

21. In G.A. MacGregor *et al.*, J. Cardiovascular Pharmacol. 7, Supp. 1, S82-87 (1985) (Exh. F hereto), the authors reported a study in which they administered captopril in combination with other antihypertensive agents. One study determined that the addition of nifedipine to patients receiving captopril resulted in a blood pressure reduction that "was significantly greater than either captopril or nifedipine alone." (*Id.*, S85.) The authors concluded that the combination of captopril with nifedipine produces additive effects and that:

> in patients with resistant hypertension [suggests that] adding nifedipine to captopril may reduce the need for diuretics, while adding captopril to nifedipine may reduce the need for beta-blockers.

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[3] "Carey dec." refers to the Declaration of Robert M. Carey dated May 14, 2010.

(*Id.*, Abstract)

22. Another article in the same publication, Mimran *et al.*, J. Cardiovascular Pharmacol. 7, Supp. 1, S92-95 (1985) (Exh. G hereto), reported a study of patients whose blood pressure was not controlled by the ACE inhibitors captopril or enalapril in combination with a diuretic. The calcium antagonist nifedipine was then added to the therapeutic regimen, which provided adequate control of hypertension. The triple therapy regimen was later modified by discontinuing the diuretic or the ACE inhibitor in certain patients. The study determined that the addition of nifedipine reduced blood pressure, the discontinuation of the ACE inhibitor increased blood pressure, and that discontinuation of the diuretic had no significant effect on blood pressure. Thus, the combination of the ACE inhibitor and the calcium antagonist controlled hypertension when the combination of the ACE inhibitor and the diuretic did not. The authors concluded that:

> . . . calcium blockers may be an effective alternative to diuretics in patients receiving a converting enzyme inhibitor.

(*Id.*, Abstract.)

23. In 1986, W. White *et al.*, Clin. Pharmacol. Ther. **39**, 43-48 (Jan. 1986) (Exh. H hereto), reported on a study of the use of captopril and the calcium antagonist nifedipine to treat patients with severe hypertension. The data showed that the combination of captopril and nifedipine reduced the patients' blood pressure more than either drug alone. The authors concluded that "combination therapy with captopril and nifedipine effectively lowers BP in patients with very severe or resistant hypertension." (White at p. 46.) Dr. Carey notes that "two [sic, three] of the patients were dosed with a third drug, furosemide." (*See* Carey dec., ¶ 13.) Dr. Carey overlooks the statement in White *et al.* that these patients were already taking furosemide for congestive heart failure before they entered the study. (Skiles dec., Exh. 9, White at p. 44-

45.) Thus, the furosemide was not prescribed to control their hypertension. Dr. Carey also misstates the results of the study, by selectively quoting the authors' conclusion. (*See* Carey dec., ¶ 13.) Dr. Carey quotes the authors' observation that three patients did not meet the therapeutic goal using the eight-hour dosing interval, but omits the authors' statement that they all responded well to a more frequent dosing regimen, and that all ten patients responded to the combination therapy.

24. The ACE inhibitors enalapril and lisinopril, introduced and tested in human subjects after captopril, were an improvement both in their side effect profiles and their durations of action. Researchers recognized what they had recognized with captopril—that they could be combined with a calcium antagonist. M.E. Vincent *et al.*, Clin. and Exper.—Theory and Practice A6(8), 1485–97 (1984) (Exh. I hereto), reported a study involving the administration of enalapril and nifedipine (a calcium antagonist.) The data presented in the paper show that nifedipine alone acted more quickly than enalapril alone, but that enalapril alone was longer-lasting. The combination of the two drugs acted more quickly than enalapril alone and the effect lasted longer than nifedipine alone. In addition, over a several-hour period, the total reduction in blood pressure was greater than the reduction attributable to each of them by itself. This additivity is shown in Figure 1, which plots the blood pressure over time for enalapril, nifedipine, and the combination of the two. It is also indicated in Table 1, which sets forth an "area under the curve" for each drug separately and for the combination. As measured in this way, the blood pressure lowering effect of the combination was approximately additive of the ACE inhibitor and the calcium antagonist. The authors suggested that their observations could be extrapolated to other ACE inhibitors, concluding:

> These data suggest that coadministration of an ACE inhibitor and calcium-entry blocker [calcium antagonist] may provide better blood pressure control than either

> drug class alone and at the same time prevent the reflex tachycardia frequently observed after nifedipine.

(*Id.*, Abstract, p. 1485.)

25. U.S. Patent 4,703,038 (the "Garthoff patent" or "Garthoff") (Exh. J hereto), was filed for in Germany in late 1984. This patent is directed to drug products that include an ACE inhibitor and a calcium antagonist and that are used for treatment of cardiovascular disease, including hypertension. Garthoff recognized that essentially any member of the entire class of ACE inhibitors could be combined with a calcium antagonist, and the patent defines the ACE inhibitors by a generic formula. As specific examples, Garthoff identifies enalapril and lisinopril as two ACE inhibitors covered by this formula. (Col. 3, ll. 21–59.) Garthoff also reported that the active compound combination can be converted into customary formulations, such as tablets, capsules or pills. (Col. 5, ll. 9–18.) The exemplified combination consists of the ACE inhibitor enalapril and the calcium antagonist nitrendipine (Table 1, col. 6, l. 9–col. 7, l. 24.) According to the animal data in the patent, the combination of enalapril and nitrendipine provides a greater reduction in blood pressure than either of the components by itself. In particular, the data in Table 1 of the Garthoff patent show that the calcium antagonist acts more quickly than the ACE inhibitor, but that the ACE inhibitor has a longer duration of action. The combination shows a greater blood pressure reduction overall, with a more rapid reduction than with enalapril alone, and a longer-lasting reduction than with nitrendipine alone. This effect is shown in Exh. K hereto, which is a plot of the difference in systolic pressure from baseline over time for nitrendipine alone, enalapril alone, and the combination of the two. The '038 patent states:

> Oral administration of nitrendipine leads to a reduction in blood pressure which is dose-dependent but is of limited duration. Although enalapril causes a lasting reduction in blood pressure in these rats, the action can be substantially increased by simultaneous administration of a small dose of nitrendipine (see table). On the other hand, administration of enalapril in addition to nitrendipine

> increases the reduction in blood pressure to over 9 hours after the administration. This means that, with an improved and extended action, the individual components can be reduced or the individual doses can be halved (see table).

(*Id.* Col. 6, ll. 20-31.)

26. Dr. Carey states that the data in Garthoff show that on the whole the combination of enalapril and nitrendipine reduce the rats' blood pressure "to about the same extent." (*See* Carey dec., ¶21.) This conclusion is not consistent with the data. The data are set forth in Exh. K hereto in graphical form, plotted as the difference in blood pressure from the control. At every point after the first few minutes and until the end of the nine-hour period, the effect of the combination is greater than that of either component. This difference is more pronounced for the systolic pressure than the diastolic pressure, but is observable in both. Moreover, the area under the curve, which is an overall indication of effectiveness, is clearly greater for the combination than for either component. Dr. Carey states that the data in Garthoff show that after a number of hours after dosing, the rats' blood pressure increased towards the pre-dosing level, and that this blood pressure rise would have discouraged persons from considering this combination. In fact, the data clearly show (*see* Exh. K and Table I of the Garthoff patent) that at all times after dosing with the combination, the blood pressure was substantially lower than the pre-treatment levels. Even at nine hours, these blood pressure values, both systolic and diastolic, were almost 20 mm Hg lower than the pre-treatment values. For the first two hours, the blood pressure response to the combination was similar to that for nitrendipine monotherapy, but for the remainder of the 9 nine-hour period the blood pressure response to the combination was greater than either of the responses to the individual drugs. These data provide compelling evidence for the anti-hypertensive efficacy of combining enalapril, an angiotensin-converting enzyme inhibitor, and the calcium antagonist nitrendipine, since the blood pressure response to the combination was

clearly additive. Thus, a person skilled in the art who reviewed the Garthoff data would be encouraged to consider the combination of an ACE inhibitor and a calcium antagonist in the treatment of hypertension.

27. Thus, well before the filing date of the '244 patent, researchers had recognized the desirability of combining ACE inhibitors and calcium antagonists. The introduction into human subjects of each ACE inhibitor had been closely followed by its combination with a calcium antagonist.

28. Not only had specific ACE inhibitors been disclosed in combination with calcium antagonists, medical researchers had recognized that effective ACE inhibitors in general could be combined with calcium antagonists in general and the combinations used in antihypertensive therapy. In 1985, Alberto Zanchetti, J. Cardiovascular Pharmacol. 7, Supp. 1, S126–131, Fig. 2 (1985) (Exh. L hereto), proposed a stepped-care approach to treating hypertension which included the administration of an ACE inhibitor in combination with a calcium antagonist.

V. PRIOR ART PUBLICATIONS DISCLOSED QUINAPRIL AS AN EXCELLENT ACE INHIBITOR CANDIDATE

29. The next ACE inhibitor to be successfully introduced was quinapril. Quinapril is an ACE inhibitor covered by claim 1 of the '244 patent. In 1984, H.R. Kaplan *et al.*, Federation Proceedings **43**, 1326-29 (1984) (Exh. M hereto), reported on studies involving ACE inhibition by a compound referred to by an internal compound number "CI-906." I understand that CI-906 refers to quinapril in the form of its salt, quinapril hydrochloride. Kaplan *et al.* report on an *in vitro* study in which quinapril exhibited a higher potency of ACE inhibition compared to both enalapril and captopril. (Fig. 2 and accompanying text.) In addition, they present data from other animal studies that show that quinapril is similar in activity to enalapril. (Figs. 4 and 5 and accompanying text.) In one of the studies, the duration of action for quinapril was longer than

that for captopril. The article states that quinapril did not produce any undesirable result in other studies that were designed to "rule out undesirable pharmacologic properties and to otherwise define the overall profile[] of [this] compound[]." (p. 1329.) The authors conclude that

> CI-906 [quinapril] [is a] new, potent, orally active nonsulfhydryl angiotensin-converting enzyme inhibitor[] having a rapid onset and prolonged duration of action. [It is] active as [an] antihypertensive agent ... and [is] expected to have therapeutic utility in any other conditions where ACE inhibition would be useful.

(*Id.*, 1329.)

30. Another article in that same publication presents more information on quinapril. M.J. Ryan *et al.*, Federation Proceedings **43**, 1330–32 (1984) (Exh. N hereto), reports on animal studies comparing quinapril to other ACE inhibitors in terms of blood pressure reduction. The studies show that quinapril, administered as quinapril hydrochloride, is more potent than captopril and shows approximately the same activity as enalapril. The authors state that quinapril is a "potent, orally active antihypertensive agent[] without any limiting side effects," (*Id.*, 1330, Abstract), and conclude that:

> [Quinapril is a] new, potent, orally active antihypertensive agent[]. [Its] antihypertensive profile in several models of experimental hypertension suggests that [it] will have therapeutic utility in both renin-dependent and renin-independent forms of hypertension.

(*Id.*, 1332.)

31. Shortly thereafter, quinapril was shown to be effective in human patients. Gavras *et al.*, J. Clin. Pharmacol. **24**, 343–50 (1984) (Exh. O hereto), reports a pilot clinical trial in which the patients were administered quinapril monotherapy. The authors explained that patients taking the ACE inhibitor captopril had in the past experienced adverse reactions. Those reactions were usually attributable to the sulfhydryl group in captopril's molecule. As a result, a "second generation" of ACE inhibitors, including enalapril and quinapril, were developed that

did not contain the sulfhydryl group found in captopril. The authors reported that enalapril had been previously found to be at least as effective and apparently devoid of the adverse reactions associated with captopril. The authors identified quinapril as another member of the new nonsulfhydryl ACE inhibitors. The authors went on to report the results of their clinical trial which they believed to be the "first" study of quinipril in hypertensive patients stating that:

> Our data indicate that the nonsulfhydryl ACE inhibitor CI-906 is indeed an effective antihypertensive agent . . . the drug's potency and duration of action are similar to those of enalapril, which is also a nonsulfhydryl ACE inhibitor. Both of these agents are more potent and longer acting than captopril, although, in terms of clinical efficacy, no significant difference appears to exist between captopril and enalapril.
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> * * *
>
> In conclusion, we found that single doses of the new nonsulfhydryl ACE inhibitor CI-906 produces blood pressure and hormonal changes comparable to those of the other oral ACE inhibitors, at dosages similar to those of enalapril, without evidence of adverse reaction.

(*Id.*, 348, 349.)

32. By 1985, quinapril had generated sufficient interest in the field that it was by itself the subject of a chapter entitled "Quinapril" by Cohen, et al., in a book *New Drugs Annual: Cardiovascular Drugs*, Vol. 3, pp. 71-84 (1985) (Exh. P hereto.) Cohen stated:

> . . . [Q]uinapril has been shown to be a potent, orally active ACE inhibitor. . . . [It] will likely become a useful drug for the treatment of clinical hypertension regardless of cause. . . . Quinapril has a remarkably large margin of safety regarding both side effect laibility and toxicity. . . .
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> In summary, quinapril, a nonsulfhydryl ACE inhibitor, represents a significant advance in hypertension therapy.

(*Id.*, 81–83.)

VI. THE LEVEL OF ORDINARY SKILL IN THE ART

33. The field to which the '244 patent is directed is that of devising drug therapies for hypertension and other cardiovascular diseases. In my opinion, a person of ordinary skill is a medical scientist, such as a pharmacologist or a medical doctor involved in pharmacological research. Such a person would have an M.D. or a Ph.D. in pharmacology or a related field, and several years' experience in research in the treatment of cardiovascular disease. Such a person a would easily understand the references discussed below and would be able to draw inferences from them.

34. The '244 patent is not specifically directed to new compounds or their synthesis; all the examples involve combinations of already known drugs. Nowhere does the patent disclose the properties of any new chemical compound. For this reason, I do not believe that the '244 patent is directed to chemists involved in synthesizing new drugs. Plaintiffs assert that the person of skill in the art must be a Ph.D. chemist as well as a medical researcher because only a highly-trained chemist could understand formula I in the '244 patent claims. I do not agree that the understanding of that formula requires an advanced degree in chemistry. As of 1986, virtually everyone involved in medical research had taken organic chemistry and biochemistry courses in college or university. In the United States, all premedical students take organic chemistry in college, and medical school curricula include a course in biochemistry. Formula I by itself is relatively simple. The conventions used in the formula, using single straight lines to indicate single bonds, double lines for double bonds, the use of "R" to denote defined groups of atoms, etc., were well known to students of organic chemistry. Working through the various differently defined "R" substituents is a tedious exercise, but understanding the structures of the compounds within the scope of the formula does not require a particular knowledge of chemistry

beyond that possessed by a person who had taken a course in basic organic chemistry and had learned its concepts. In addition, part of every organic chemistry course involves learning the nomenclature that organic chemists use. A person skilled in the art who did not remember the meaning of a particular chemical term included in the claim was certainly capable of looking it up in an organic chemistry textbook.

35. I know personally and by reputation most of the senior authors referred to in the papers discussed above. All of them are physicians engaged in clinical research. None of them is an organic chemist.

VII. OBVIOUSNESS OF THE CLAIMS OF THE '244 PATENT

36. The only difference between the invention of claim 1 of the '244 patent and the combinations discussed in the prior art is that the latter do not disclose a compound within the scope of Formula I of the claim. Instead, the prior art specifically discuss the combinations of calcium antagonists with ACE inhibitors captopril, enalapril, and lisinopril, which are outside the scope of Formula I. The only difference between the invention of claim 1 of the '244 patent and the Vincent and Garthoff publications is that the latter describe the use of enalapril or lisinopril as the ACE inhibitor. Similarly, the only difference between the invention of claim 1 of the '244 patent and the Stornello, MacGregor, Brouwer, Mimran and White articles is that the latter describe the use of captopril as the ACE inhibitor. Captopril, enalapril and lisinopril, although widely prescribed ACE inhibitors, are outside the scope of Formula I.

37. Although captopril, enalapril and lisinopril are outside Formula I in claim 1, quinapril is covered by that formula. In my opinion, a person of ordinary skill in the art would have found it obvious to employ quinapril instead of captopril, enalapril or lisinopril in the combinations disclosed in Vincent, Garthoff, Stornello, MacGregor, Brouwer, Mimran,

Zanchetti and White. Those references teach the desirability of combining an ACE inhibitor and a calcium antagonist, and the information available for quinapril indicates that it was a good candidate to be the ACE inhibitor in such a combination. Vincent and Zanchetti in particular refer to the combination of calcium antagonists and compounds within the "class" of ACE inhibitors. Quinapril is certainly within that class. A person of ordinary skill in the art would have recognized that others skilled in the art had disclosed that a number of prior ACE inhibitors that had been used in humans had also been suggested for use with a calcium antagonist. When a study with quinapril suggested that it would likewise be safe and effective for humans, the person skilled in the art would also have expected that the combination of quinapril and a calcium antagonist would be effective to reduce patients' blood pressure and therefore to treat a patient's hypertension. Indeed, in view of the suggestions in the literature that quinapril was likely to exhibit significant advantages over captopril and was at least as promising as enalapril, a person skilled in the art would have been motivated to employ quinapril in the combinations with calcium antagonists with a reasonable expectation of success that a quinapril/calcium antagonist combination would be effective for the treatement of hypertension.

38. Claim 1 also refers to a "pharmaceutical composition." Although the human studies with combinations of captopril and a calcium antagonist and enalapril and a calcium antagonist referred to above do not employ fixed dose combinations in single tablets. Fixed dose combinations of antihypertensive drugs were well known in 1986, and it would have been self-evident to combine the drugs in that way for patient convenience. Moreover, Garthoff discloses making fixed dose combinations of ACE inhibitors and calcium antagonists.

39. Claims 2 depends from claim 1 and limits the scope of the set of ACE inhibitors, but it still claims encompasses quinapril and quinapril hydrochloride as described in the Kaplan, Ryan and Gavras articles:

> **2. A composition according to claim 1, wherein:**
> **n=1 or 2,**
> **R is (C_1–C_6)-alkyl, (C_2–C_6)-alkenyl, (C_3–C_9)-cycloalkyl, or (C_6–C_{12})-aryl,**
> **R^1 is hydrogen, (C_1–C_6)-alkyl, (C_2–C_6)-alkenyl, (C_3–C_9)-cycloalkyl, (C_5–C_9)-cycloalkenyl, (C_3–C_7)-cycloalkyl-(C_1–C_4)-alkyl, (C_6–C_{12})-aryl or partially hydrogenated aryl,**
> **or a side chain of a naturally occurring, optionally protected α-amino acid,**
> **R^2 and R^3 are the same or different and are hydrogen, (C_1–C_6)-alkyl, or (C_2–C_6)-alkenyl, and**
> **R^4 and R^5 are as defined in claim 1.**

Claim 3 depends from claim 1 and limits the ACE inhibitors to trandolapril or quinapril and their physiologically acceptable salts:

> **3. A composition according to claim 1, wherein said ACE inhibitor is 1-[N-(1-S-ethoxycarbonyl-3-phenylpropyl)-S-alanyl]-(2S,3aR,7aS)-octahydro[1H]indole-2-carboxylic acid (trandolapril) or a physiologically acceptable salt thereof, or 2-[N-(1-S-ethoxycarbonyl-3-phenylpropyl)-S-alanyl]-1,2,3,4-tetrahydroisoquinoline-3-S-carboxylic acid (quinapril) or a physiologically acceptable salt thereof.**

40. Claim 4 is directed to the composition of claim 1 but additionally requires that the amounts of ACE inhibitor and calcium antagonist in combination are effective for simultaneous, separate or periodic regulated use in the treatment of high blood pressure. The Stornello, MacGregor, Brouwer, Mimran, White and Garthoff references all disclose that their combinations are useful in the treatment of hypertension, i.e., high blood pressure, and provide simultaneous dosing information (e.g., Garthoff patent (Exh. J), col. 4, ll. 61-64; col. 5, ll. 4-17; col. 6, ll. 20-50.)

41. Claim 7 is directed to a method for the treatment of high blood pressure comprising administering to a host in recognized need thereof a pharmaceutical composition according to claim 1. The Garthoff patent discloses that ACE inhibitor/calcium antagonist combinations can be administered to patients for the treatment of high blood pressure, cardiac insufficiency, and coronary heart disease. (Col. 4, ll. 61–64; col. 5, ll. 4–17; col. 6, ll. 20–50.) For this reason, the subject matter of claim 7 would have been obvious.

42. I do not interpret "treatment of hypertension" in claim 1 and "treatment of high blood pressure" in claim 7 to mean different things. Most medical texts and dictionaries define "hypertension" as "high blood pressure," and most medical professionals do not make a distinction between the two terms in everyday parlance. Nothing in the '244 patent suggests that "hypertension" means anything other than "high blood pressure."

43. Claim 10 is directed to the composition of claim 1 but additionally requires that it further comprise a physiologically acceptable carrier. The Garthoff patent discloses that the combinations can be converted to administrable formulations using inert, pharmaceutically suitable excipients or solvents. (Col. 5, ll. 9–14.)

44. Drs. Carey and Piepho state that because hypertension, once it becomes manifest, is generally not reversible, any agent or combination of agents "effective for treating hypertension" must be a regimen that will work for months or years. (*See* Piepho dec., ¶ 25; Carey dec., ¶ 23.) A drug that successfully lowers the blood pressure of a hypertensive patient for a week or a month treats the disease for that length of time, and administering the drug for that length of time is treating hypertension. Moreover, the literature uses "treatment" and "treating" to describe short term studies. *See, e.g.*, Stornello ("treatment"); Brouwer ("treatment period," "treatment regimen"); Mimran ("treatment"). Indeed, many hypertensive patients begin

their treatment regimens using one drug or drug combination and later switch to another because the first no longer controls blood pressure adequately. The person of ordinary skill in the art would have a reasonable expectation based on the studies disclosed in the prior art that an ACE inhibitor/calcium antagonist combination would be effective for treating hypertension.

45. Drs. Piepho and Carey state that a person skilled in the art would essentially ignore the articles describing successful use of the captopril/calcium antagonist combinations and the Gavras article because all of them involved relatively few patients. (*See* Piepho dec., ¶ 15; Carey dec., ¶ 14.) According to Drs. Piepho and Carey, such small studies cannot show statistical significance or be used to draw consistent conclusions about the results. (*See* Piepho dec., ¶ 17; Carey dec., ¶¶ 12 and 14.) The medical literature includes many reports of small studies. Such reports are often valuable notwithstanding their lack of statistical power. Although they may not "prove" the effectiveness or non-effectiveness of a particular therapy, they provide useful indications and insights. All the papers referred to above appeared in peer-reviewed publications, and many were authored by highly respected clinician-scientists. A person skilled in the art would not have disregarded them; instead he or she would have found them encouraging and would have been motivated to consider such combination therapy in appropriate circumstances. Anyone who considered such therapy would consider other ACE inhibitors, including quinapril, as they were developed.

46. Drs. Piepho and Carey have argued that meaningful differences exist between ACE inhibitors. (*See* Piepho dec., ¶¶ 41-56; Carey dec., ¶¶ 54-61.) They allege that therefore a person of ordinary skill would not have been able to predict how these differences could affect the activity of any ACE inhibitor in combination with a calcium antagonist. Drs. Piepho and Carey have relied on several publications to support their statements that ACE inhibitors should

not be treated as a class. (*See* Skiles dec., Exh. 13-23 and 46-47.) These articles were published between 1989 and 2008 and are not relevant to whether a person of ordinary skill would have considered ACE inhibitors to be a single class of drugs in October 1986. Moreover, although these articles point out differences among various ACE inhibitors, the articles themselves make clear that these differences are much less significant than the drugs' similarities, particularly that all act in the same way to lower blood pressure. Also, nothing in the literature or in medical experience in 1986 would have suggested that an ACE inhibitor would act any differently in combination with a calcium antagonist than it would by itself. The expectation of a person skilled in the art would have been that an ACE inhibitor having certain therapeutic properties when used alone would retain those properties when used in combination with a calcium antagonist.

47. Dr. Winkler points out that by 1986 many ACE inhibitors had been tested for ACE inhibiting activity in addition to quinapril. (*See* Winkler dec., ¶¶ 32-38.)[4] This observation suggests that not only would the quinapril/calcium antagonist combination have been obvious, but so would many others. In any event, many of these compounds were at the time untested *in vivo*, and of those that had been tested *in vivo*, only a very few had been tested in human patients and found to be effective. A person skilled in the art considering combinations of ACE inhibitors and calcium antagonists would naturally have considered first the ACE inhibitors that had already been used safely and successfully in humans. Combinations of captopril, enalapril and lisinopril with calcium antagonists were disclosed in the prior art. Of the others, quinapril was the most frequently discussed compound in the literature, and was the compound that would have occurred first to the person skilled in the art.

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[4] "Winkler dec." refers to the Declaration of Jeffery D. Winkler dated May 14, 2010.

48. For this reason, the selection of quinapril for a combination with a calcium antagonist is not finding a needle in a haystack. It would have been the most logical choice at the time.

49. Dr. Winkler makes much of the fact that the various ACE inhibitors had different molecular structures and that these differences would lead to different chemical and pharmacological effects that perhaps could not have been predicted *a priori*. (*See* Winkler dec., ¶¶ 9-26.) Whether or not he is correct is irrelevant here, however, since the properties of quinapril as an ACE inhibitor had been explored and published before October 1986. Thus, quinapril was already known to reduce blood pressure in animals and humans and had been shown to be safe enough for study in human patients. Regardless of whatever differences exist between its molecular structure and that of enalapril, its biological effects were known to be quite similar. The extent to which a person skilled in the art could have predicted that similarity beforehand is not pertinent to whether a person skilled in the art would have conceived the concept of combining quinapril with a calcium antagonist once its efficacy and safety had been shown.

50. The person of ordinary skill in the art, while recognizing that the known ACE inhibitors differed in their chemical structure, would have been primarily interested in their *in vivo* properties, including their toxicity and their ability to inhibit ACE and lower blood pressure. Thus, they would have given little consideration to the differences in chemical structure between ACE inhibitors whose biological properties had already been determined.

51. The subject matter of claims 1–4, 7 and 10 of the '244 patent would have been obvious to the person of ordinary skill in the art prior to September 1986.

VIII. OBVIOUSNESS IN VIEW OF THE CLAIMED INVENTION OF U.S. PATENT NO. 5,098,910

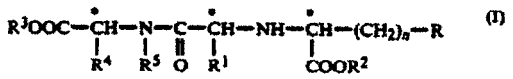
A. The '910 patent

52. I have reviewed and considered the '910 patent and its file history in forming my opinions. The specification of the '910 patent is substantially the same as that of the '244 patent.

53. Claim 1 of the '910 patent defines a pharmaceutical composition whose active ingredients are an ACE inhibitor as defined by the claim and any calcium antagonist:

1. A pharmaceutical composition, comprising pharmaceutically synergistically effective amounts of

a) an angiotensin-converting enzyme inhibitor (ACE inhibitor) of the formula I



(I)

in which

n = 1 or 2,

R = hydrogen,

an optionally substituted aliphatic radical with 1–8 carbon atoms,

an optionally substituted alicyclic radical with 3–9 carbon atoms,

an optionally substituted aromatic radical with 6–12 carbon atoms,

an optionally substituted araliphatic radical with 7–14 carbon atoms,

an optionally substituted alicyclic-aliphatic radical with 7–14 carbon atoms,

a radical OR^1 or SR^1, wherein

R^1 represents an optionally substituted aliphatic radical with 1–4 carbon atoms, an optionally substituted aromatic radical with 6–12 carbon atoms or an optionally substituted heteroaromatic radical with 5–12 ring atoms,

R^1 is hydrogen,

an optionally substituted aliphatic radical with 1–6 carbon atoms,

an optionally substituted alicyclic radical with 3–9 carbon atoms,

an optionally substituted alicyclic-aliphatic radical with 4–13 carbon atoms,

an optionally substituted aromatic radical with 6–12 carbon atoms,

an optionally substituted araliphatic radical with 7–16 carbon atoms,

an optionally substituted heteroaromatic radical with 5–12 ring atoms or

the side chain, protected if necessary, of a naturally occurring α-amino acid,

R^2 and R^3 are the same or different and are hydrogen,

an optionally substituted aliphatic radical with 1–6 carbon atoms,

an optionally substituted alicyclic radical with 3–9 carbon atoms,

an optionally substituted aromatic radical with 6–12 carbon atoms, or

an optionally substituted araliphatic radical with 7–16 carbon atoms and

R^4 and R^5 together with the atoms carrying them form an optionally substituted octahydrocyclopenta pyrrole ring system, or a physiologically acceptable salt thereof, and

b) a calcium antagonist or a physiologically acceptable salt thereof.

The formula for the ACE inhibitor in claim 1 encompasses ramipril, but excludes quinapril and trandolapril.

54. Claim 4 of the '910 patent defines a pharmaceutical composition of claim 1 wherein the ACE inhibitor is limited to ramipril.

> A composition as claimed in claim 1, wherein said ACE inhibitor comprises 1-[N-(1-ethoxycarbonyl-3-phenylpropyl)-S-alanyl]-3aS,6aS)-octahydroncyclopenta[b]pyrol-2-S-carboxylic acid or a physiologically tolerated salt thereof.

55. Claim 9 of the '910 patent defines a pharmaceutical composition of claim 1 for the treatment of high blood pressure:

> The pharmaceutical composition of claim 1 wherein the amounts of said ACE inhibitor, or salt thereof, and calcium antagonist, or salt thereof, in combination are synergistically effective for simultaneous, separate or periodic regulated use in the treatment of high blood pressure.

56. Claim 10 of the '910 patent defines a method for treating high blood pressure by administering a pharmaceutical composition of claim 1:

> A method for the treatment of high blood pressure, which comprises administering a pharmaceutical composition as claimed in claim 1.

57. By October 1986, ramipril had been tested in patients, and these tests indicated that ramipril was an orally effective antihypertensive ACE inhibitor with a long duration of action. (*See* Bohm, et al., *Eur. Jrnl. Clin. Pharmacol.* 30: 541-47 (1986), Exh. Q hereto.)

B. The Subject Matter Of Claims 1-4, 7 And 10 Of The '244 Patent Would Have Been Obvious In View Of Inventions of Claims 4, 9 Or 10 Of The '910 Patent

58. The only difference between the invention of claim 1 of the '244 patent and that of claim 4 of the '910 patent is that the latter does not disclose a compound within the scope of the former. Instead, claim 4 discloses the combination of the ACE inhibitor ramipril with a calcium antagonist, and ramipril is outside the scope of Formula I.

59. In my opinion, a person of ordinary skill would have found it obvious to employ quinapril instead of ramipril in the combination disclosed in claim 4 of the '910 patent. Claim 4 discloses that ramipril is an ACE inhibitor which can be combined with a calcium antagonist. The prior art disclosed that Vincent, Garthoff, Stornello, MacGregor, Brouwer, Mimran, Zanchetti and White teach the desirability of combining an ACE inhibitor and a calcium antagonist, and the information available for quinapril indicates that it was a good candidate to be the ACE inhibitor in such a composition. Vincent and Zanchetti in particular refer to the combination of calcium antagonists and compounds within the "class" of ACE inhibitors. Quinapril is certainly within that class. A person of ordinary skill in the art would have a reasonable expectation of success that the combination of quinapril and a calcium antagonist would work to reduce the patient's blood pressure.

60. Both claims 2 and 3 of the '244 patent depend from claim 1 and limit the scope of ACE inhibitors, but both claims still encompass quinapril and quinapril hydrochloride as described in the Cohen, Kaplan, Ryan and Gavras articles. Thus, the subject matter of these claims would also have been obvious in view of claim 4 of the '910 patent.

61. The subject matter of claim 4 of the '244 patent would have been obvious in view of the invention of claim 9 of the '910 patent. Claim 4 of the '244 patent is directed to the composition of claim 1 but additionally requires that the amounts of ACE inhibitor and calcium antagonist in the combination are effective for simultaneous, separate or periodic regulated use in the treatment of high blood pressure. Claim 9 of the '910 patent is directed to the composition of claim 1 and similarly requires that the amounts of ACE inhibitor and calcium antagonist are synergistically effective for simultaneous, separate or periodic regulated use in the treatment of high blood pressure. In addition, the Stornello, MacGregor, Brouwer, Mimran, White and

Garthoff references all disclose that their combinations are useful in the treatment of hypertension, i.e., high blood pressure, and provide simultaneous dosing information. (e.g., Garthoff patent (Exh. J), col. 4, ll. 61–64; col. 5, ll. 4–17; col. 6, ll. 20–50.)

62. Claim 7 of the '244 patent is directed to a method for the treatment of high blood pressure comprising administering to a host in recognized need thereof a pharmaceutical composition according to claim 1. Claim 10 of the '910 patent is similarly directed to a method for the treatment of high blood pressure comprising administering a pharmaceutical composition as claimed in claim 1. In addition, the Garthoff patent discloses that ACE inhibitor/calcium antagonist combinations can be administered to patients for the treatment of high blood pressure, cardiac insufficiency, and coronary heart disease. (Col. 4, ll. 61–64; col. 5, ll. 4–17; col. 6, ll. 20–50.) For these reasons, the subject matter of claim 7 would have been obvious in view of the invention of claim 10 of the '910 patent.

63. Claim 10 of the '244 patent is directed to the composition of claim 1 but additionally requires that it further comprise a physiologically acceptable carrier. The Garthoff patent discloses that the combinations can be converted to administrable formulations using inert, pharmaceutically suitable excipients or solvents. (Col. 5, ll. 9–14.)

64. The subject matter of claims 1-4, 7 and 10 of the '244 patent would have been obvious to the person of ordinary skill in the art prior to September 1986 in view of the inventions of claims 4, 9 or 10 of the '910 patent.

IX. ABSENCE OF UNEXPECTED RESULTS

A. Dr. Carey's and Dr. Piepho's Comparisons are Not With the Closest Prior Art or are Not Commensurate with the Scope of the Claims

65. In reaching my conclusions on obviousness, I have considered whether there are any unexpected properties of the subject matter. I understand that unexpected properties must be

established by factual evidence. I also understand that any alleged unexpected properties must be unexpected with respect to the closest prior art to the claims. I further understand that a showing of unexpected results must be commensurate with the scope of the claims.

66. These claims cover a variety of ACE inhibitor/calcium antagonist combinations including the trandolapril/verapamil combination found in TARKA.

67. I have identified Garthoff, Vincent, Brouwer, White, Stornello, MacGregor, and Mimran, as reporting prior art ACE inhibitor/calcium antagonist combinations. Of these the closest prior art to claims 1–4, 7 and 10 are Garthoff and Vincent, which each describe an enalapril/calcium antagonist combination. Such combinations are closer than the captopril/calcium antagonist combinations because quinapril and trandolapril are closer to enalapril in structure and properties than they are to captopril.

68. I am aware that plaintiffs' experts, Drs. Carey and Piepho, alleged several categories of unexpected properties. (*See* Piepho dec., ¶¶ 57-69; Carey dec., ¶¶ 62-81.) These included contentions that the trandolapril/verapamil combination:

(i) reduced proteinuria;

(ii) delayed the onset of diabetes;

(iii) was glycemically neutral;

(iv) was synergistic in black patients;

(v) was longer acting than prior art ACE inhibitor/calcium antagonist combinations;

(vi) had an unexpected superadditive effect on reducing blood pressure;

(vii) improved blood vessel structure and function; and

(viii) reduced the incidence of cardiac events.

69. Drs. Carey and Piepho cited a number of references to support their contention of unexpected properties. In my opinion, none of these references supported the claim of unexpected results for several reasons. The first reason is that none of these references report a comparison between a combination covered by the claims of the '244 patent and any prior art ACE inhibitor/calcium antagonist combination. Absent such a comparison, the evidence does not support any inference that the claimed combination provides any unexpected results. The second reason is that none of the comparisons encompass the scope of the claims of the '244 patent. Claim 3 is the narrowest claim, but it still covers many combinations, and the alleged unexpected results are all related only to TARKA, a particular fixed dose combination of trandolapril and verapamil sustained release.

B. TARKA Does Not Exhibit Surprising Activity or Duration of Action

70. Dr. Piepho asserts that TARKA exhibits superadditivity, and he cites as evidence TARKA NDA, Report No. MPF/KP-9105, which reports a study conducted in Stroke Prone Spontaneously Hypertensive Rats (SPSHRs). (*See* Piepho dec., ¶¶ 62-63, 65; Skiles dec., Exh. 28.) The data in this report is unreliable and in any case does not show that TARKA had a more than additive antihypertensive effect compared to its individual monotherapies. My analysis is as follows:

a. Dr. Piepho did not present the data from the first day of the study. The antihypertensive effect can be quantified by comparing the area under the curve ("AUC") for the trandolapril/verapamil combination to the individual monotherapies of trandolapril and verapamil administered separately. As expected, these data showed that the antihypertensive effect of the combination was greater than for either verapamil or trandolapril alone, but less than the sum of the individual effects. The AUC of the trandolapril and verapamil combination was

[redacted] *See* Table 2a at ABT001129. Thus, the data showed the antihypertensive effect of the trandolapril/verapamil combination was additive of the individual monotherapies.

b. I regard as unreliable the data on superaddativity of the trandolapril verapamil combination, which is only reported for the 29th day of the study. On this day, which followed several days of continuous treatment, all treatment groups were reported to have an essentially identical initial blood pressure. In a properly controlled experiment, there is no rational explanation for these results. I have reproduced part of this data in the table below. *See* Table 1 at ABT001128.

[redacted]

It would be reasonable to expect the initial blood pressures to have been substantially lower for the active treatment groups than for the control group. They are not.

c. Moreover, a close examination of the data indicates that the antihypertensive effect of the combination was additive of the monotherapies. Table 1 and Figure 1 at ABT001128 shows on the 29th day of treatment that the blood pressure fall in response to verapamil was from [redacted] The sum of these effects is [redacted] The corresponding value for the

[redacted] Taking into account the large variance of the data indicated by the values for the standard error of the mean, the BP reduction in the rats treated with the combination cannot be said with any confidence to be greater than that in the rats treated with verapamil or trandolapril alone.

d. The blood pressure in the SPSHRs increases with age and weight. The average age and weight of the animals in each group is not provided. Without this information it is not possible to determine whether the different groups have a comparable average age and weight or a very different average age and weight. In the former case, the groups would have a similar blood pressure in the absence of treatment. In the latter case, the groups would have different blood pressure in the absence of treatment, and the results of this study would be unreliable.

71. Dr. Piepho cited to Knoll's CA Patent No. 2,103,666 as reporting the superadditivity of the verapamil SR and trandolapril combination in conscious normotensive dogs, hypertensive rats and patients with high blood pressure. (*See* Piepho dec., ¶¶ 64-65; Skiles dec., Exh. 29.) However, no data are presented so it is not possible to confirm the veracity of these claims.

72. Dr. Piepho fails to mention that the TARKA NDA also disclosed [redacted] (*See* TARKA NDA, ABT 000670-677, Exh. R hereto.) Although animal data are useful in studying the effects of antihypertensive drugs, the human data when available, are more relevant to whether TARKA has an unexpected antihypertensive effect in patients than the study in rats cited by Dr. Piepho.

73. [redacted] (*See* ABT 000672.) [redacted] I have reproduced the data from this study below.

[redacted]

74. [redacted] It is generally accepted that the trough blood pressure is a more reliable measure of the sustained 24 hour efficacy of antihypertensive medications, and

more reliance is placed on these data than those for peak blood pressure. Moreover, the FDA approved TARKA label states "[v]erapmil hydrochloride and trandolapril have been used individually and in combination for the treatment of hypertension. The antihypertensive effects of these agents are approximately additive." (*See* TARKA NDA at ABT000418, Exh. S hereto.)

75. [redacted] (*See* ABT 000676.) [redacted]

76. [redacted] is an expected and predictable result of administering a trandolapril/verapmil combination.

77. Dr. Piepho cites Klein as claiming that a combination of captopril and nifedipine (a CCB) had no significant additive effect on blood pressure. (*See* Piepho dec., ¶ 66; Skiles dec., Exh. 30.) I disagree with Dr. Piepho's interpretation of this paper. Klein described a cross-over study in 26 patients with mild to moderate essential hypertension. The combination of both drugs was only administered to the ten patients who did not respond to monotherapy. The lack of additive effect was due to the selection of these monotherapy-resistant subjects for the combination therapy. However, there was a statistically significant effect of the combination therapy in the monotherapy-nonresponders attributable to the addition of the second drug.

78. Dr. Piepho mistakenly concluded that Vincent did not disclose an additive effect because the peak effect for administering the combination enalapril and nifedipine was not significantly different than for nifedipine alone; and, after several hours, the blood pressure of the enalapril and nifedipine combination was only slightly lower than that of nifedipine alone. (*See* Piepho dec., ¶ 24 and ¶ 67; Exh. I hereto.) Dr. Piepho ignored the overall blood pressure lowering effect over the entire experiment. This result is presented as the AUC in Table 1 and clearly showed that the integrated systolic blood pressure response for the combination was approximately the sum of that of each drug given individually. Thus, enalapril alone lowered the systolic blood pressure 214 $\pm$ 74 mm Hg · hr; nifedipine alone 207 $\pm$ 67 mm Hg · hr; and the combination 372 $\pm$ 89 mm Hg · hr. *See* Vincent at page 1491.

79. Mancia did not claim that TARKA had a surprisingly long duration of action. Dr. Piepho suggested that TARKA has a superior trough-to-peak ratio than the monotherapies. (*See* Piepho dec., ¶ 58; Skiles dec., Exh. 24.) Mancia reports that the trough-to-peak ratio for TARKA was 0.54 for systolic blood pressure at the 8th week of treatment. *See* Mancia at page 496. One would expect that the peak blood pressure response to the combination would be greater than that of the individual components alone. The fact that this is not so for the peak systolic blood pressure of the combination is sufficient to explain the higher trough-to-peak ratio of the combination compared to the monotherapies.

80. In my opinion, Dr. Piepho has misinterpreted Donnelly. (*See* Piepho dec., ¶ 59; Skiles dec., Exh. 25.) Donnelly did not compare, or suggest a comparison between the combination of enalapril/nicardipine and TARKA. Donnelly compared a combination of enalapril/nicardipine with a combination of enalapril/chlorthalidone and concluded that the former had a shorter half life than the latter. Chlorthalidone is known to have a half life of 40-60

hours. (*See* 2004 CLORPRES package insert, Exh. T hereto.) Nicardipine has a half life of 8.6 hours. (*See* 1991 CARDENE® package insert, Exh. U hereto.) The fact that the enalapril/nicardipine combination was not as well sustained at 24 hours compared to the enalapril/chlorthalidone combination was due to the shorter half life of nicardipine as compared to chlorthalidone. This was recognized by the authors, who stated as follows: "[h]owever, blood pressure control with the combination of enalapril and nicardipine was significantly attenuated during the latter part of a dosage interval, presumably as a reflection of its relatively short half-life and duration of action, and additionally was less sustained at 24 hr." (*See* Donnelly at page 845.)

81. The description of the daily dosing of LEXXEL and TECZEM by Drs. Piepho and Carey is incorrect. (*See* Piepho dec., ¶¶ 60-61; Carey dec., ¶¶ 62-63.) They stated that LEXXEL and TECZEM are or may be taken twice a day. However, the label for LEXXEL states that in clinical trials of enalapril-felodipine ER the combination therapy was used once daily. (Skiles dec., Exh. 26.) The label for TECZEM states that it is formulated as a once-a-day extended release tablet. (Skiles dec., Exh. 27.) Further, the only reference to twice daily administration is for the enalapril mono-component of LEXXEL and TECZEM. (Skiles dec., Exh. 27.) TARKA is also given once a day. (*See* TARKA package insert, Exh. V hereto.) There is no difference in the dosing schedule between TARKA, LEXXEL and TECZEM.

C. Tarka's Ability To Reduce Proteinuria Is Not A Surprising Or Unexpected Property

82. Dr. Carey opined that TARKA's ability to reduce proteinuria was an unexpected and surprising property. (*See* Carey dec., ¶¶ 71-73.) For the reasons set forth below, this property of TARKA is neither surprising nor unexpected, and does not distinguish TARKA from the prior art.

83. Proteinuria is an important indicator of kidney disease. Meta-analyses of randomized clinical trials have evaluated the utility of ACE inhibition therapy in renal protection and slowing the rate of progression of renal disease. ACE inhibitors slow the progression of renal disease, decrease protein excretion, slow the rate of increase in serum creatinine, and reduce the risk of end-stage renal disease. (*See* Chiurchiu et al., Journal of the American Society of Nephrology, 2005, 16(3) Suppl 1:S58-63, Exh. W hereto.)

84. Some CCBs, namely verapamil and diltiazem, have also been shown to be effective in reducing urinary albumin excretion. Combination therapy of an ACE inhibitor and a CCB has been shown to have an additive effect on reduction of proteinuria independent of blood pressure. (*See* Ritz, American Journal of Hypertension, 1995, 8:53S-58S, Exh. X hereto.)

85. Dr. Carey relied on of Bakris (1998), Rubio-Guerra and Munter for their opinion that TARKA had a surprising ability to reduce proteinuria. (Skiles dec., Exhs. 53-55.) None of the results disclosed in Bakris (1998), Rubio-Guerra or Munter showed that reducing proteinuria was a surprising or unexpected property of TARKA. Other ACE inhibitor/CCB combinations also reduce proteinuria.

86. For example, Toto found that a trandolapril/verapamil SR fixed-dose combination was no better than the ACE inhibitor/CCB combination of benazepril/amlodopine for reducing albuminuria. (*See* Toto et al., The Journal of Clinical Hypertension, 2008, 10(10):761-9, Exh. Y hereto.) In a study of type 2 diabetics with hypertension and nephropathy, both treatments reduced albuminuria, and there was no difference in the magnitude of reduction in albuminuria between the treatment regimens. *See* Toto at pages 765-66. According to the authors of the study, this suggested that administration of either regime could effectively reduce albuminuria in type 2 diabetics with hypertension and nephropathy. *Id.*

87. Stornello reported a study using the combination of captopril and nicardipine in diabetic patients. (*See* Stornello et al., J Cardiovasc Pharmacol. 1989 Dec;14(6):851-5, Exh. Z hereto.) Stornello examined the effect of nicardipine (a CCB), captopril, and the combination of the two on blood pressure and renal function. They reported that the combination of nicardipine and captopril reduced urinary albumin excretion to a greater extent than either monotherapy. *See* Figure 3 at page 854.

88. Bakris (1992) reported a study with the combination of lisinopril and verapamil. (*See* Bakris et al., Kidney Int. 1992 Apr;41(4):912-9, Exh. AA hereto.) Bakris investigated the effect of this combination in type 2 diabetic patients with kidney disease. These patients were divided into groups which received one of the following treatments: an ACE inhibitor, lisinopril (group I); a calcium antagonist, sustained release verapamil (group II); and the combination (group III). A fourth group received hydrochlorothiazide and guanfacine (group IV). The authors explained that blood pressure was equally reduced in all groups. Following one year of therapy, the greatest reduction in urinary albumin excretion among all groups occurred in the group receiving the combination therapy, group III (68%). The results for group III, were significantly better than for groups I, II and IV which had respectively a 55, 47 and 8% reduction in urinary albumin excretion. The study shows that the combination of lisinopril and verapamil is superior to either agent alone for reducing urinary albumin excretion in this population.

89. Thus, TARKA's antiproteinuric property was not a surprising or unexpected property because it did not distinguish TARKA from the prior art or other ACE inhibitor/CCB combinations.

D. Tarka Does Not Have The Unexpected Property Of Delaying The Onset Of Diabetes And Its Neutral Effect On Glucose Metabolism Is Not An Unexpected Property

90. Dr. Carey stated that surprisingly TARKA did not impair glucose metabolism. (*See* Carey dec., ¶¶ 77-80.) He also stated that TARKA surprisingly delayed the risk of diabetes. (*See* Carey dec., ¶¶ 74-76.) He supported his statements with citations to studies which compared TARKA with diuretics and/or β-adrenergic antagonists. However, diuretics and β-adrenergic antagonists both impair glycemic control and accelerate the onset of diabetes. ACE inhibitors and calcium antagonists, alone or in combination, by comparison, will outperform diuretics and β-adrenergic antagonists in this regard. Thus, there is nothing surprising or unexpected in the relative glycemic neutrality of TARKA.

91. Several studies have shown that diuretics and β- adrenergic antagonists increase the risk of diabetes and impair glucose metabolism.

92. Bengtsson published a longitudinal study of hypertensive women patients that concluded that there was a considerable increased risk in developing diabetes for subjects with hypertension who were taking diuretics, β-adrenergic antagonists and a combination of diuretics and β-adrenergic antagonists compared with subjects not taking antihypertensive drugs. (*See* Bengtsson et al., Br Med J (Clin Res Ed.) 1984 289(6457):1495-7, Exh. BB hereto.)

93. Bloomgarden published a study comparing, among other things, the HbA1c levels of insulin-treated diabetic patients receiving HCTZ, the loop diuretic furosemide, or no diuretic. (*See* Bloomgarden et al., Am J Med. 1984 ;77(5):823-7, Exh. CC hereto.) The study found that HbA1c levels were 7.2 ± 1.8 % with HCTZ; 5.9 ± 2.3% with furosemide, and 6.4 ± 2.0% with no diuretic. Twelve percent of the patients receiving HCTZ had HbA1c below 5%, as opposed to those 26% receiving no diuretic. Of those patients receiving HCTZ, 32 % had HbA1c levels

over 8.0%, as opposed to 22% on no diuretic. The authors concluded that the treatment with thiazide-diuretics was associated with higher levels of glycosylated hemoglobin in a group of insulin treated diabetic patients.

94. Elliott undertook a systematic review of 22 clinical trials with 143,153 participants who did not have diabetes at the outset. (*See* Elliott et al., Lancet 2007 369(9557):201-7, Exh. DD hereto.) The outcome examined was the proportion of patients who developed diabetes. They concluded that the association of antihypertensive drugs with new diabetes was lowest for angiotensin receptor blockers (ARB) and ACE inhibitors; followed by CCB and placebo; followed by β- adrenergic antagonists and diuretics, in rank order. The authors stated that diuretics and β-adrenergic antagonists apparently increased the risk of diabetes whereas ACE inhibitors reduced the risk. (*Id.*, p. 205, col. 2.)

95. Grossman reported that β-blockers and diuretics have been well-documented to have a negative effect on insulin sensitivity. (*See* Grossman et al., Adv Cardiol. 2008;45:82-106, Exh. EE hereto.) By contrast, ACE inhibitors reduce the occurrence of new-onset diabetes. (*Id.*, p. 93. Grossman also reported that calcium antagonists, particularly verapamil and diltiazem, decrease proteinuria. (*Id.*, p. 94.)

96. These analyses were not limited to high dose diuretics. The reviews of Elliott and Grossman cover the periods up to and including 2007-2008, which is several decades after it was realized that high dose thiazide diuretics had adverse metabolic effects. These reviews still report an increased risk of the development of diabetes in patients treated with thiazide diuretics at lower doses. Thus, they refute Dr. Carey's assertion that only high dose diuretics decrease insulin sensitivity and increase the risk of diabetes.

97. Dr. Carey cited Holzgreve as having shown that TARKA was glycemically superior to other antihypertensive combinations. (*See* Carey dec., ¶ 78, Skiles dec., Exh. 59.) Holzgreve compared TARKA to atenolol/chlorthalidone in type 2 diabetic patients to determine their effect on glucose metabolism by measuring HbA1c. TARKA maintained HbA1c at 7.9% while the combination of atenolol/chlorthalidone raised HbA1c from 7.8% to 8.6%. Holzgreve clearly stated that this was not surprising because thiazide diuretics and β-blockers were known to decrease insulin sensitivity and impair glucose metabolism whereas ACE inhibitors were known to potentially improve insulin sensitivity.

> There has been concern over adverse effects of thiazide diuretics and β blockers in diabetic patients, since both agents decrease insulin sensitivity and impair glucose tolerance. The influence on glycemic control might be even more pronounced by combinations of these agents. Calcium channel blockers and angiotensin converting enzyme inhibitors are considered to lack these undesirable effects on glucose tolerance. Angiotensin converting enzyme inhibitors potentially improve insulin sensitivity.

(*See* Holzgreve at p. 381, col. 1.) Predictably, the combination of trandolapril and verapamil outperformed the combination of atenolol and chlorthalidone because the latter was known to impair glucose metabolism.

98. Dr. Carey also cited Schneider as showing that TARKA was metabolically neutral, while insulin resistance worsened with a combination of the β-blocker atenolol and the diuretic chlorthalidone. (*See* Carey dec., ¶ 78, Skiles dec., Exh. 60.) Schneider compared TARKA to atenolol/chlorthalidone in type 2 diabetic patients. According to Schneider their findings were consistent with previous studies which showed that β-blockers and diuretics reduced insulin sensitivity whereas ACE inhibitors and CCBs minimally improved or left insulin sensitivity unchanged.

> Thus, these findings during two drug-combination treatments complement previous observations of a reduced insulin sensitivity during mono-therapies with

> different β-blockers or diuretics and of a minimally improved or unchanged insulin sensitivity during controlled studies of angiotensin converting enzyme inhibitors or of different calcium antagonists other than nifedipine in non-diabetic and (studied less often) in diabetic hypertensives.

(*See* Schneider at page 675, col. 1.) Thus, according to Schneider, ACE inhibitors and calcium antagonists predictably outperform diuretics and blockers in regard to insulin sensitivity.

99. Dr. Carey also cited the relative improvements in glucose control seen with TARKA in the Fernandez study. (*See* Carey dec., ¶ 80, Skiles dec., Exh. 62.) Fernandez compared TARKA to enalapril in combination with a diuretic, HCTZ, for the ability to maintain glucose control. Diabetic patients were randomized to treatment with TARKA or enalapril/HCTZ. Of the TARKA patients, 29.5% had improved glucose control while 6.8% had worse glucose control. Of the patients taking enalapril/HCTZ 13.6% had improved glucose control while 11.4% had worse glucose control. However, according to the authors their study showed that when the antihypertensive response to an initial ACE inhibitor was inadequate, adding a non-DHP calcium antagonist was preferable to low dose diuretic. Thus, the only conclusion to be drawn from Fernandez is that all ACE inhibitor/CCB combinations outperform ACE inhibitor/ diuretic combinations.

> There is increasing concern regarding the metabolic effects of antihypertensive drug therapy and their impact on cardiovascular risk reduction resulting from the treatment of hypertension. Hypertensive subjects taking beta-blockers or diuretics, or both, have an increased risk of diabetes compared to hypertensive subjects not taking those agents. Diuretics, at least in high doses, have been associated with glucose intolerance. Thiazide-induced glucose intolerance is related to development of insulin resistance. In contrast, calcium channels [sic] blockers do not appear to alter insulin sensitivity. Adverse effect of diuretics on glycaemic control is reflected on a rise in serum glucose and glycated haemoglobin levels … A recent review of clinical trials indicates that most hypertensive patients with diabetes require more than one agent to achieve blood pressure control. The choice of the second antihypertensive agent could influence the risk of these patients. The data in this paper support the recommendations offered by this recent consensus, in which it is suggested that, after the initial ACE inhibition therapy, adding a non-DHP calcium channel blocker or low-dose

> thiazide diuretic offers an augmented benefit for further blood pressure reduction. The initial level of HbA1c in our patients (5.93%) is to be noticed; although starting from an excellent metabolic situation, the different effect on metabolic control between the combinations compared in this trial suggests for the first time that when blood pressure response to the initial ACE inhibitor is inadequate, adding a non-DHP calcium antagonist can be preferable to low-dose diuretic.

(*See* Fernandez at 854, col. 2.)

100. Dr. Carey cited a number of studies in which TARKA was compared to other drugs with respect to their effect on glycemic control and diabetes. In all cases, thiazide diuretics or β-blockers were included in the comparator group.

101. In INVEST, the comparators were atenotol and HCTZ. (*See* Carey dec., ¶ 74; Skiles dec., Exs. 56-57.) In STAR and STAR-LET, the comparators were losartan and HCTZ. (*See* Carey dec., ¶ 75-77 and 79; Skiles dec., Exhs. 58 and 61.)

102. Cooper-DeHoff was the lead author of an analysis of the INVEST data applied to the development of diabetes in patients with coronary artery disease, which confirmed that β-blockers and diuretics were more frequently associated with diabetes than ACE inhibitors and CCBs. (*See* Carey dec., ¶ 74; Skiles dec., Exh. 57)

> Many trials have suggested that, compared with an angiotensin active drug or calcium antagonist, β blockers and/or diuretics are more frequently associated with DM [diabetes] development. Similar to INVEST, many of these trials included additional antihypertensive drugs. The increased risk for DM we observed with atenolol and hydrochlorothiazide and decreased risk with trandolapril added to verapamil SR are consistent with several of these previous studies.

(*See* Copper-DeHoff at page 893 at col. 2.)

103. These results are not surprising in view of the meta-analysis performed by Elliott which showed that β-blockers, such as atenolol, and diuretics, such as HCTZ, are both more likely to increase the risk of diabetes. *Supra.* ACE inhibitors as a class reduce the risk. Thus, rather than being surprising, the outcome was predictable.

104. Moreover, from the perspective the person of ordinary skill in September 1986, it would not be surprising that a patient treated with a β-blocker, such as atenolol, or a diuretic, such as HCTZ or chlorthalidone, would be at higher risk of developing diabetes or have poor glucose control because the studies of Bloomgarden and Bengtsson suggest this would be the result. *Supra.* It would not be surprising or unexpected that patients being treated for high blood pressure with a β-blocker and/or a diuretic would be more likely to develop diabetes than patients treated with an ACE inhibitor/CCB combination. The person of ordinary skill in the art would therefore not find any of the results presented in the papers cited by Dr. Carey to be unexpected.

E. Tarka Does Not Show An Unexpected Synergistic Effect In Black Patients

105. Dr. Carey cited a study by Skoularigis for showing that TARKA had a synergistic effect in black patients. (*See* Carey dec., ¶ 66, Skiles dec., Exh. 49.) Synergism implies that the effect observed with TARKA was greater than the sum of the effects with the monotherapies of trandolapril and verapamil. In fact, there was no evidence from Skoularigis that TARKA was synergistic because TARKA was not compared to the monotherapies verapamil and trandolapril.

106. The Skoularigis study was conducted on 21 patients with mild to moderate hypertension. After a 14-day wash-out period and a 14-day placebo run-in period, therapy was initiated with verapamil 180 mg plus trandolapril 2 mg. At monthly visits, if mean daytime diastolic BP remained at or above 90 mmHg, the dose combination was increased stepwise to verapamil 240 mg plus trandolapril 4 mg, verapamil 360 mg plus trandolapril 4 mg, and finally HCTZ 12.5 mg could be added. After 4 months of treatment the mean 24-hour blood pressure dropped from 150 ± 14/ 96 ± 7 mmHg to 131 ± 13/ 82 ± 8 mmHg.

107. There was no evidence from Skoularigis that TARKA was synergistic because TARKA was not compared to the monotherapies of verapamil and trandolapril. There also was no evidence from this study that TARKA was better than an other ACEI/CCB combination.

108. Moreover, Dr. Carey mischaracterized the conclusion as set forth by the authors. Dr. Carey stated in his report that "[i]n addition, they also concluded that 'it is reasonable to suggest' that Tarka was 'synergistic in these hypertensive patients' (*Id.*, 55.)". The authors never made that statement. Instead they said that verapamil plus ACE inhibition may be synergistic.

> From the present results it is reasonable to suggest that the combination of verapamil plus ACE inhibition may be synergistic in these hypertensive patients, as our results in monotherapeutic studies with ACE inhibitor in a similar group showed little antihypertensive effect ....

See Skoularigis at page 55. Thus, the authors concluded that ACE inhibitors as a class may be synergistic in combination with verapamil in this population.

109. Dr. Carey cited Goodman, a paper which I co-authored, as suggesting that black patients may not respond well to drugs, such as ACE inhibitors and β-blockers, that interfere with the renin-angiotensin system because blacks may have lower plasma renin activity. (*See* Carey dec., ¶ 67; Skiles dec., Exh. 50.) Dr. Carey then stated that "as shown in the Skoularigis study, Tarka is particularly effective in black patients and shows not only that there is no class effect of ACE inhibitors but also that all ACE inhibitors are not alike." Skoularigis did not reach the conclusion suggested by Dr. Carey. Skoularigis at page 55. If anything, Skoularigis suggested that ACE inhibitors were to be treated as a single class, and any member of that class, when combined with verapamil, would likely give synergistic results in this patient population.

110. The fact that TARKA lowers blood pressure in black patients tells us nothing about the effects of the components on blood pressure in this group. Since there is evidence that black patients are less sensitive to the antihypertensive effects of ACE inhibitors, it is reasonable

to conclude that the blood pressure lowering effect of TARKA is attributable primarily to its verapamil component. Dr. Carey did not cite any study which compared TARKA with its individual components in black patients. The only study in which reference to that comparison is made is Skoularigis et al. Skoularigis examined the effect of the combination of trandolapril and verapamil in black patients and found that after four months of treatment the mean 24 hr BP fell from 150 ± 14 / 96±7 mmHg to 131± 13/ 82 ± 8 mmHg, a decrease of 19/14 mmHg. There is no monotherapy comparator in the Skoularigis study. There is, however, a reference to unpublished data with sustained-release verapamil alone in 10 black hypertensive patients where there was a decrease in blood pressure of 9/5 mmHg. It is, however, quite unacceptable to use the verapamil monotherapy data as controls for the combination therapy since the number of subjects is small, and there is no information concerning the inclusion criteria, the duration of the study, and the baseline demographics of the study subjects. These data, therefore, do not invalidate the notion that the response in blood pressure to ACE inhibitor/verapamil combination in black patients is driven primarily by verapamil.

F. The Trandolapril And Verapamil Combination Does Not Synergistically Improve Blood Vessel Structure And Function

111. Dr. Carey cited a study by Versari for showing that TARKA synergistically improved blood vessel structure and function. (*See* Carey dec., ¶ 68-69; Skiles dec., Exh. 51.) The aim of the Versari study was to evaluate the effect of treatment with verapamil, trandolapril and their combination on peripheral microcirculation vasoreactivity. The authors concluded "that chronic treatment with verapamil ameliorates endothelial function in the forearm microcirculation of essential hypertensive patients, while trandolapril protects microcirculation from structural alterations." *See* page 214; *See* Versari at Abstract.

112. According to Dr. Carey, the results of this trial "showed that the 'combination of verapamil and trandolapril, as compared to single drugs, synergistically improves blood vessel structure and function'". However, according to Versari his study supported a more general conclusion regarding the mechanism of action of ACE inhibitor/CCB combinations. In discussing the outcome of this study, Versari states

> "[t]hese differential, and partly additive-beneficial effects exerted by these two different compounds support a potential synergistic benefit derived from the combination of ACE-inhibitors and CCB. Previous works clearly demonstrated the benefical effect of dihyrdrophyridines nifedipine...lacidipine... and lercandipine...in improving endothelium-dependent vasodilation, virtually leading to a normalization of endolthelial function in the peripheral microcirculation of essential hypertensive patients...These findings are in line with a large amount of data showing a high efficacy of ACE-inhibitors in inducing a regression of vascular structural changes in the forearm microcirculation...as well as in subcutaneous small arteries."

See Versari at 5-6.

113. The ability of ACE inhibitors as a class, and calcium antagonists as a class, to improve the structure and function of small arteries has been reviewed, *inter alia*, by Schiffrin and Galdarasi. (*See* Schiffrin, Am J Med Sci 2001; 2001;322(1):7-11, Exh. FF hereto; Galdarasi et al., J. cardiovasc. Pharmacol. 2008 51(6):523-531, Exh. GG hereto.) In both, it is made clear that improvements in arterial structure and function are a class effect of ACE inhibitors and calcium antagonists. "Treatment of SHR with antiotensin I-converting enzyme (ACE) inhibitors, angiotensis II receptor antagonists, or calcium antagonists, is associated with improvement of endothelial dysfunction and correction of remodeling of small arteries. Increased collagen deposition in the media of small vessels was also decreased by treatment." *See* Schiffrin at page 8.

114. Since both classes of agents are effective in improving arterial structure and function, it is not an unexpected result that the combination of trandolapril and verapamil should do so.

G. The Trandolapril And Verapamil Hcl Combination Does Not Unexpectedly Reduce Cardiac Events To A Greater Extent Than Trandolapril Alone

115. Dr. Carey cites Hansen as supporting the conclusion that cardiac events are reduced by the trandolapril and verapamil HCl combination to a greater extent than trandolapril alone. (*See* Carey dec., ¶ 70; Skiles dec., Exh. 52.) However, Hansen reports only on the cardiac event rate in post-infarct patients with congestive heart failure patients already prescribed diuretics. In these patients, trandolapril plus verapamil reduced the three month first cardiac event rate compared to trandolapril alone.

116. These patients are a very specific subset of patients at risk for cardiac events and therefore, it is not reasonable to extrapolate from these data to the reduction of cardiac events in general. According to Hansen, in the Danish infarction trial DAVIT II "the 18-month mortality rate in postacute myocardial infarction (AMI) patients without congestive heart failure (CHF) was lower in verapamil-treated than placebo-treated patients...." *See* Hansen at page 738. Additional support for the utility of CCBs is given by a meta-analysis of 147 randomized trials on the use of blood pressure lowering drugs in the prevention of cardiovascular disease (Law et al. BMJ 2009; 338:1665 (Exh. HH), in which it is concluded that the major determinant of the prevention of cardiovascular events is blood pressure lowering – somewhat independent of the class of antihypertensive drug used. A beneficial effect in preventing coronary heart disease events, and strokes is found with both ACE inhibitors and CCBs.

117. Hansen hypothesized that his results were generic to ACE inhibitor/verapamil combinations. He stated that in post-infarct patients with congestive heart failure who were

already prescribed diuretics and an ACE inhibitor, additional treatment with verapamil might reduce cardiac event rate. *Id.* In the Abstract, Hansen et al. stated that "[t]hese data suggest that verapamil reduces cardiac event rates in post-AMI [acute myocardial infraction] patients with CHF [congestive heart failure] when added to an ACE inhibitor and a diuretic." *Id.* Hansen did not state that the trandolapril/ verapamil combination was unexpectedly better than other ACE inhibitor/CCB combinations.

118. Therefore it would not be unexpected that the combination of trandolapril and verapamil would improve outcomes in post-myocardial infarction patients since there is abundant evidence to support the efficacy of ACE inhibitors and CCBs in this situation.

X. PROSECUTION OF THE '244 PATENT

119. I have been provided with a copy of the '244 patent prosecution history. I am advised that this document is a record of the communications between the applicants for the '244 patent and the United States Patent and Trademark Office that led to the allowance of the claims of the '244 patent. I have reviewed and considered the prosecution history of the '244 patent in formulating my opinions.

120. In particular, I have reviewed the Office Action that bears the date April 19, 1996, on the last page (Paper No. 5, attached hereto as Exh. II.) In that paper, the patent examiner rejected the pending claim of the application "under 35 U.S.C. § 103 as being unpatentable over Garthoff et al. (A)." I understand that the "Garthoff" to which the examiner was referring is equivalent to the Garthoff patent discussed above. I am advised that the examiner's statement means that he was rejecting the claim on grounds that the invention would have been obvious to a person of ordinary skill in the art in view of Garthoff.

121. The examiner went on to state:

> The claim appears to be drawn to a composition comprising an ACE inhibitor and a calcium antagonist. Garthoff et al. teaches a combination comprising ACE inhibitors and the calcium antagonist dihydropyridines . . . . The claim differs from the reference in claiming other ACE inhibitors to be used in the composition. To use other ACE inhibitors would have been obvious given the close structural relationship between the compounds of the reference and the compounds of the claim. The claim fails to patentably distinguish over the state of the art as represented by the cited reference.

(Exh. II hereto, p. 3.) In my opinion, the examiner was correct that it would have been obvious to substitute other ACE inhibitors in the combination of Garthoff.

122. In response to this statement, the applicants stated:

> . . The ACE inhibitors disclosed by Garthoff are not structurally similar to those presently claimed. Specifically, claim 1 is directed to ACE inhibitors containing a heterocyclic **bicyclic or tricyclic** ring system. Garthoff, in contrast, teaches ACE inhibitors having only **monocyclic** proline ring systems, which are not structurally similar to bicyclic and tricyclic ring systems.
>
> Moreover, Garthoff neither teaches nor suggests that its monocyclic ring systems can or should be substituted with polycyclic systems. Garthoff provides no motivation to one skilled in the art to modify its ACE inhibitors to arrive at those of claim 1 as amended. Thus, Garthoff in no way renders obvious the pharmaceutical composition of claim 1.

(Amendment dated August 23, 1996, p. 5; Exh. JJ hereto; emphasis in original.)

123. In my opinion, applicants' statement quoted above, as well as the examiner's apparent acceptance of it, does not reflect either the knowledge available in the art or the way in which people skilled in the art viewed these compounds. A person skilled in the art would not be particularly concerned with differences between the detailed chemical structures of the claimed ACE inhibitors of Garthoff and those of the '244 patent. ACE inhibitors within the scope of Garthoff, e.g., enalapril, and ACE inhibitors within Formula I of the '244 patent, e.g., quinapril, were already known and already known to be effective. The salient point to a person skilled in the art is that all the compounds belong to the same class of drugs: ACE inhibitors. All have the

same therapeutic indication and operate in the same way to affect it. Thus, the issue is not whether it would have been obvious to "modify the structure" of the Garthoff ACE inhibitors, but instead whether it would have been obvious to use another known ACE inhibitor instead of enalapril, the exemplary compound of Garthoff. The Kaplan, Ryan and Gavras references show that people skilled in the art compared those compounds head-to-head because they recognized that the compounds are in the same class – ACE inhibitors. Likewise, Vincent and Zanchetti suggested the combination of "an ACE inhibitor," rather than an ACE inhibitor having a specific molecular structure. Accordingly, it would have been obvious to substitute enalapril with quinapril, and the expectation of a person skilled in the art would have been that the combination was safe and effective.

* * *

I declare under penalty of perjury that the foregoing is true and correct.

May 24, 2010

Clive Rosendorff, M.D., Ph.D., D.Sc.Med.